CASE

Spinal segmental myoclonus in both legs associated with antibodies to glycine receptors

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Glycine receptors (GlyR) are distributed in the adult nervous system, where they mediate fast inhibition.[1] GlyR is composed of 3 alpha and 2 beta subunits, and null mutation in these subunits results in hyperekplexia, excessive startle responses, and muscle rigidity. Progressive encephalomyelitis with rigidity and myoclonus (PERM), characterized by muscle rigidity, myoclonus, hyperekplexia, autonomic disturbance, and brainstem dysfunction, is also associated with antibodies to glycine receptors (GlyR-Abs). We describe a patient with PERM associated with GlyR-Abs who had synchronized spinal segmental myoclonus in both legs.

PRACTICAL IMPLICATIONS

Antibodies to glycine receptors were associated with synchronized myoclonus in both legs and the myoclonus derived from not only the brainstem but also the spine.

Case report

A 69-year-old man was given a diagnosis of intestinal follicular lymphoma. At 72 years of age, he had difficulty walking, subsequently followed by the onset of dysphagia and vocal cord paralysis. He received steroid pulse therapy (1 g/d, 3 days) because of positive anti-lipoprotein receptor-related protein 4 (Lrp4) antibodies and antibiotics because of aspiration pneumonia. Acetylcholine receptor antibodies, muscle-specific kinase antibodies, and the results of IV edrophonium testing and repetitive nerve stimulation were normal. These features gradually improved, and the Lrp4 antibodies became negative. Difficulty in swallowing recurred 6 months and 1 year later, and steroid pulse therapy resolved the swallowing dysfunction. At 74 years of age, the patient noticed hypertonia and bilateral synchronous myoclonus in the legs. The myoclonus progressed, and supranuclear type of neurogenic bladder also developed, requiring the placement of a ureteral catheter, leading to admission to our hospital. He was well-oriented. There was no motor weakness or sensorial or cranial nervous impairment. Rigidity was evident in the legs. Deep tendon reflexes were increased in the legs with no Babinski sign. Surface EMG showed that both the tibialis anterior and gastrocnemius muscles simultaneously and synchronously contracted (video 1), and average duration of 7 EMG bursts was 264.6 ± 14 ms. The myoclonus was easily elicited by other external stimuli and responded well to diazepam (10 mg/d). The patient could not stand or walk because of the frequent myoclonus. Somatosensory evoked potentials (SSEPs) were normal with no giant SSEP. The results of EMG and EEG were normal. Cranial and spinal MRI were normal. Multiple lymphomatous polyps were found on colonoscopy, and intestinal follicular lymphoma was pathologically diagnosed. The results of serum laboratory and CSF examinations were normal. Anti-GlyR antibodies were positive in serum and CSF on cell-based assay. Antibodies to anti–glutamic acid decarboxylase, amphiphysin, gephyrin, Ri, Yo, Hu, CV2, Ma2, recoverin, SOX1, titin, zic4, Tr, voltage-gated potassium channel, voltage-gated calcium channel, and gangliosides were negative. He received steroid pulse therapy twice (1 g/d, 3 days) and IV immunoglobulin (400 mg/kg/d, 5 days). The myoclonus resolved, and the urinary catheter was withdrawn. He could walk without an assistant. Two months later, bilateral ptosis and diplopia developed. The results of repeated examinations for myasthenia gravis were negative, indicating that these features were derived from PREM. He received steroid pulse therapy, and the symptoms resolved. One year later, subjective mild stiffness in his legs persisted. Written informed consent was obtained from the patient for these routine clinical examinations, treatments, and publication of the case report.

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Discussion

Co-contraction in both legs of our patient slowly and simultaneously developed on the background of no marked brainstem or upper body symptoms. The EMG burst duration was within the period between 150 and 1,000 ms, supporting the spinal segmental myoclonus,[2] and there was no giant SSEP. We believed that the myoclonus in our patient might have a spinal generator. GlyR are predominantly distributed on the cell surface of postsynaptic neurons in not only the brainstem, but also the spinal cord. GlyR-Abs are predominantly immunoglobulin G (IgG)1 or IgG3 subclass[3] and bind to the extracellular domain of GlyR.[4] Patient IgG caused internalization on HEK293 cells expressing GlyR.[3] This would be expected to inhibit the GlyR and decrease glycinergic neurotransmission, resulting in loss of brainstem and spinal inhibition.[3] In patients with hereditary hyperekplexia, disynaptic reciprocal inhibition depending on glycinergic neurotransmission is observed in the spinal cord.[4] Pathologic studies in patients with PERM have shown perivascular lymphocyte cuffing and infiltration as well as neuronal loss in the spinal cord.[5] GlyR-Abs are paraneoplastic in approximately 10% of patients. In our patient, the direct association between intestinal follicular lymphoma and GlyR-Abs was uncertain since there was no apparent progress of intestinal follicular lymphoma when PERM developed. The response to immunotherapies is generally limited,[4] but myoclonus in our patient responded to immunotherapies, as reported previously.[3] GlyR-Abs cause myoclonus derived from not only the brainstem but also the spine, and the spinal segmental myoclonus can be bilaterally synchronized.

Author contributions

H. Nanaura: drafting/revising the manuscript, data acquisition, study concept or design, analysis or interpretation of data, statistical analysis. H. Kataoka: drafting/revising the manuscript, data acquisition, study concept or design, analysis or interpretation of data. T. Kiriyama: data acquisition, acquisition of data. N. Eura: data acquisition. N. Iwasa: data acquisition. R. Shobatake: data acquisition. H. Horikawa: data acquisition. K. Sugie: study concept or design, analysis or interpretation of data.

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Practical Implications

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